# Exhibit 5

10/13 T.Wms 9/29/00

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | |
|---|---|---|
| In the **PATENT APPLICATION** of: | | |
| | Lo et al. | |
| **Application No.:** | 09/380,696 | Our File: SHP-PT048 |
| **Filed:** | November 29, 1999 | Date: September 15, 2000 |
| For: NON-INVASIVE PRENATAL DIAGNOSIS | | |
| Group: | 1655 | |
| Examiner: | J. Enewold | |

**REPLY PURSUANT TO 37 C.F.R. § 1.111**

Commissioner for Patents
Washington, D.C. 20231

Sir:

This Reply is responsive to the Examiner's Action dated April 18, 2000. The Applicants respectfully request that the Application be amended as follows:

**IN THE ABSTRACT**

Please delete the abstract from the face sheet of the PCT published application and substitute therefor the ABSTRACT submitted herewith on a separate sheet.

**IN THE DRAWINGS**

A proposed revision to separately identify the individual graphs of Figure 4 as indicated in red on the attached sheet is submitted herewith.



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**Applicant:** Lo et al.
**Application No.:** 09/380,696

**IN THE SPECIFICATION**

On page 8, line 14, please delete "Figure 4 shows" and insert -- Figures 4a-4l show --.

On page 29, line 2, please delete "fig. 4" and insert -- Figures 4a-4l --.

On page 31, line 14, please delete "fig. 4" and insert -- Figures 4a-4l --.

On page 34, line 19, please delete "Figure 4" and insert -- Figures 4a-4l --.

**IN THE CLAIMS**

Please amend the following claims:

9 10. (Amended) The method according to claim 8 wherein the non-Y sequence is a blood group antigen gene [such as the Rhesus D gene].

B1

10 9. (Amended) The method according to claim 8, wherein the non-Y sequence is a gene which confers a disease phenotype in the foetus [, such as the Rhesus D gene].

Please add the following new claims:

26 27. The method according to claim 10 9, wherein the blood group antigen gene is the rhesus D gene.

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CONT B2

28. The method according to claim 10, wherein the gene is the rhesus D gene.--

## REMARKS

The drawings have been objected to because the views of Figure 4 were not labeled separately. Approval of the proposed drawing changes as indicated on the attached sheet is requested. No new matter has been added.

Applicants have amended the specification to conform with the drawing amendment. An abstract on a separate sheet has been provided as required. No new matter has been added.

Claims 1-26 are pending in the application. A priority claim to GB9704444 (hereinafter "the priority document"), filed March 4, 1997, was objected to with respect to Claims 7-8, 17, 20-21 and 24. Claims 1-26 were rejected under the first paragraph of 35 U.S.C. §112. Claims 10-11were rejected under the second paragraph of 35 U.S.C. §112. Claims 7 and 17 were rejected under 35 U.S.C. §102(a) as being anticipated by Lo (Lancet, August 1997).

Applicants respectfully traverse the Examiner's priority objection and anticipation rejection of claims 7 and 17 over Lo (Lancet, August 1997). With respect to claims 8, 20-21 and 24, the objection is not ripe since no rejection over intervening art has been made. With



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respect to the Examiner's assertion that claim 7 is not supported by the priority document because it includes no reference to detecting DYS14, Applicants respectfully disagree. Page 8, lines 2-5 of the priority document explicitly refer to amplification of a single copy of Y sequence DYS14.

With respect to claim 17, the Examiner asserts that the priority document does not disclose variations of fetal DNA concentrations over the different stages of gestation. Applicants respectfully disagree. Applicants submit that the priority document clearly describes that variations in the quantity of foetal DNA may occur in some pregnancy-associated conditions such as pre-eclampsia. Specifically, page 2, lines 24-27, specifically refers to differing amounts of foetal DNA being present in the maternal serum or plasma. One skilled in the art would readily understand that this would refer to a variation of foetal DNA concentration at a particular stage of gestation. Further, at the priority filing date, one skilled in the art would have also been aware that foetal DNA generally shows a variation over the course of a pregnancy. In order to monitor whether there is a higher or lower level of foetal DNA compared to normal, it would be desirable to make a comparison with a sample from a similar stage of gestation.

Although the priority document does not include identical claims as now on file, Applicants respectfully submit that the disclosure of the priority document, as read by one skilled in the art, clearly encompasses rejected claims 7 and 17. Accordingly, the §102 rejection based on Lo (Lancet, August 1997) is traversed as not being prior art to these claims.

The rejection of Claims 1-5 and 9-11 under the first paragraph of 35 U.S.C. §112, as containing subject matter which was not adequately described in the specification, is respectfully traversed. The Examiner contends that there is not adequate description for the detection of the large genus of paternally-inherited non-Y sequences. Although, as noted by the Examiner, there is substantial variability among the species of nucleic acids encompassed in the scope of the claim, Applicants submit that one skilled in the art is aware of a variety of techniques which might be used to detect different nucleic acid species. For example, there are numerous techniques which might be used to detect repeat expansions, single gene mutations, deletions or translocations. These techniques are a matter of routine for one skilled in the art for the analysis of DNA.

Further, the invention does not rely on the identification of any specific paternally-inherited non-Y sequences. The invention resides in the identification of foetal DNA in a serum or plasma sample. One skilled in the art could take advantage of the present

application describing the presence of foetal DNA in the plasma or serum and apply it to the detection of paternally-inherited non-Y sequences in addition to those which are described. For example, the Examiner has referred to an article by Amicucci et al. which clearly describes detection of an expanded repeat. The Amicucci et al. article clearly demonstrates that the technique as described in the present application may be readily applied to the detection of repeat sequences.

Additionally, Applicants refer the Examiner to a number of other documents which describe analysis of foetal DNA in maternal plasma or serum. Attached herewith are copies of Pertl et al. *Human Genetics* 106(1) - 45-49, 2000 (Abstract), Tang et al. *Clinical Chemistry* 45, 11;1999; 2033-2035, Smid et al. *Clinical Chemistry* 45, 8; 1999; 1570-1572 and Chen et al. *Prenat Diagn* 2000, 20; 355-357. Each of these articles provides an example of the application of the general technique described in the present application to specific sequences. Each of these articles refers to the work done by the inventors of the present application disclosed in Lo et al. In particular, these articles refer to Lo et al. where it describes detection of foetal DNA in maternal plasma and serum and describes the technique to a variety of different sequences. Moreover, the articles cited above demonstrate that microsatellite alleles which differ by a very small number of nucleotides between the mother and baby, that is by 2 base pairs, are detectable using the technology described in the present

application. Microsatellites are essentially polymorphic pieces of DNA, which are different between different individuals by virtue of insertions or deletions of a small number of base pairs. The paper by Chen et al. describes the successful diagnosis of a paternally-inherited reciprocal translocation.

Additionally, there are numerous types of mutations that might be detected, in accordance with the present invention. The Examiner has discussed whether the technique is applicable for detecting small differences between the mother and foetus and has highlighted three categories, namely, single gene mutations, deletions, and translocations. The attached articles clearly demonstrate that a wide variety of different polymorphisms may be detected in accordance with present application. Applicants submit that there is sufficient description in that the key features of the claimed technique have been described in the Application, and, in particular, one skilled in the art is instructed to use maternal plasma or serum for the detection of foetal DNA. Although there are a wide variety of different types of polymorphisms which could be detected in connection with the present application, such polymorphisms and techniques for analysis of DNA are simply a matter of routine for one skilled in the art. Therefore, it is not necessary for the Applicants to set out each of the many ways in which DNA might be analyzed. The description is sufficient simply by instructing one skilled in the art to carry out a suitable analysis. The additional documents, attached

hereto, clearly demonstrate that one skilled in the art is readily able to apply the teachings of the present application to any one of the well known techniques for detection of DNA with a view to analysis of foetal DNA in paternal plasma or serum.

Applicants respectfully traverse the rejection of Claims 1-26 under the first paragraph 35 U.S.C. §112, on the basis of lack of enablement for a general detection method performed on serum or plasma for detecting fetal nucleic acid at any time during pregnancy or associated with disease phenotype and serum. The Examiner refers to Lo et al. (*New England J. of Med.*, Vol. 339, No. 24, pages 1734-8) and suggests that the claims are only enabled with respect to detecting the presence of paternally-inherited foetal DNA in maternal plasma after 15 weeks of gestation. The Examiner has indicated that there is unpredictability in detecting foetal DNA in plasma before the fifteenth week of gestation. However, Applicants respectfully submit that the specification is enabled across the scope of the breadth of the claim for a detection method performed on serum or plasma of pregnant women to detect any foetal DNA during the course of pregnancy. Although the article cited by Examiner suggests that reliable results for foetal RHD status can be determined from the fifteenth week of gestation, the paper nevertheless demonstrates that testing prior to 15 weeks of gestation is already useful.

The Examiner has cited some of the Applicants' own comments in the article of Lo et al., *Annals of Medicine*, Volume 31, 5: 1999; 308-312. As with all technologies, it can be expected that improvements in the technology may arise. For example, it is likely that improvements will be made to enhance sensitivity of the techniques. However, this is not to say that the techniques can not be used as a diagnostic method across the scope of the claims. Clearly, the statements quoted by the Examiner in the *Annals of Medicine* cannot be seen as a suggestion that the technique does not in itself work effectively.

With respect to the dividing line of 15 weeks, the article by Lo et al. referred to by the Examiner merely states that for RHD, PCR tests are reliable beginning in the second trimester. This is not to say that such tests can not be useful when carried out before the second trimester. For example, if a potential problem were highlighted in a test carried out before the second trimester, this problem could be used as part of a diagnosis such as to identify women who require close monitoring in later stages, for example to confirm a provisional diagnosis. Thus, it may be possible to identify such things as a foetus at risk of foetal hemolytic disease before 15 weeks of pregnancy and highlight that pregnancy for enhanced surveillance.

There are also numerous papers showing that the technology can be used prior to the 15th week of gestation. In Lo et al., *American Journal of Human Genetics* of 1998, 62; 768-

775, the authors show that foetal DNA can be detected from maternal serum at the seventh week of gestation. Amicucci et al. demonstrates that the technology can be used at the tenth week of gestation. Smid et al., *Clinical Chemistry* 1999, 45;1570-1572 demonstrates that the method is applicable between the seventh and fourteenth weeks of gestation.

Additionally, the Examiner also refers to a number of papers as suggesting that there are potential problems with the technique and that to a certain extent the claims are based on hypothesis. As highlighted above, the present invention results in the new identification that foetal DNA is present in maternal plasma or serum. Many of the points highlighted by the Examiner would be considered to be a matter of routine experimentation to one skilled in the art of DNA detection, to identify the most appropriate technique for a particular required diagnosis. The person skilled in the art has a broad range of techniques available for the detection of DNA in a sample. Thus, one skilled in the art, equipped with the teaching of the present patent application, would be readily able to overcome any such potential problems mentioned by the Examiner. Indeed, there is much literature, such as the articles referred to above, which demonstrates that the technique has been successfully applied to other sequences.

The Examiner further suggests that there may be a problem in connection with using material serum and that increased amount of maternal DNA can be found. The Examiner quotes Lo et al.:

> The results indicated that a higher maternal background is present when serum is used which may be detrimental for the detection of foetal DNA, especially when less sensitive detection methods are used.

Applicants submit that one skilled in the art would understand simply that a higher maternal background may be present where serum is used, and that it may be preferable to use a more sensitive detection method. However, as highlighted above, this statement does not in any way suggest that the technique can not be used. The statement merely suggests that the technique should be optimized given the particular circumstances. This is simply a straightforward matter of application of an appropriate DNA detection method.

The Examiner has highlighted some problems in using serum samples, highlighted by Bischoff et al. However, one skilled in the art would simply take appropriate action to avoid the specific problems highlighted in this article. The article does not suggest that the method would in any way not work simply because serum DNA was being used. In any event, there are a number of papers which have used maternal serum reliability for detection of foetal DNA, namely, Lo et al. *American Journal of Human Genetics* Supra, Lo et al., *Clinical Chemistry* 1999, 45;184-188 (abstract attached).

In summary, the, various documents cited by the Examiner do not suggest that the present technique would not be successful. Improvement of the process or selection of the most appropriate of DNA analysis is simply a matter of routine experimentation which would be carried out by one skilled in the art based on the readily available techniques of DNA detection.

With respect to the rejection of Claims 10 and 11 under 35 U.S.C. §112, Applicants have amended these claims to delete the phrase "such as" objected to by the Examiner. New dependent claims 27 and 28 have been added. Applicants believe these claims are now in condition for allowance.

It is respectfully submitted that the pending claims as amended are now in condition for allowance. Reconsideration, approval of the drawing amendment, and allowance are respectfully requested.

**Applicant:** Lo et al.
**Application No.:** 09/380,696

Respectfully submitted,

Lo et al.

By _____
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1617 John F. Kennedy Boulevard
Philadelphia, PA 19103

CFK/JMO/dag

Attachments: Pertl et al. *Human Genetics*
Tang et al. *Clinical Chemistry*
Smid et al. *Clinical Chemistry*
Chen et al. *Prenat Diagn*
Lo et al., *American Journal of Human Genetics*
Lo et al., *Clinical Chemistry*

Enclosures (2)

## ABSTRACT

The invention relates to a detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample. The invention enables non-invasive prenatal diagnosis including for example sex determination, blood typing and other genotyping, and detection of pre-eclampsia in the mother.

Fig. 4

#11

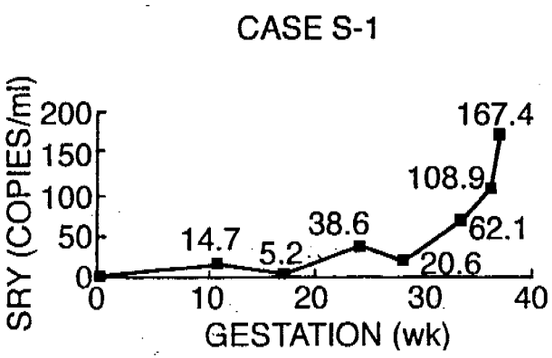


Fig. 4a

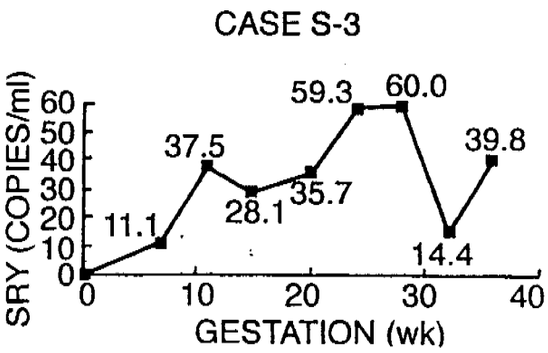


Fig. 4b

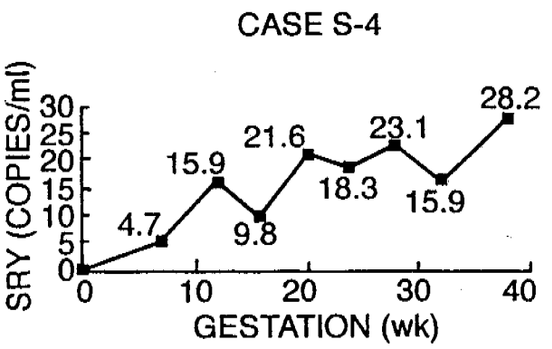


Fig. 4c

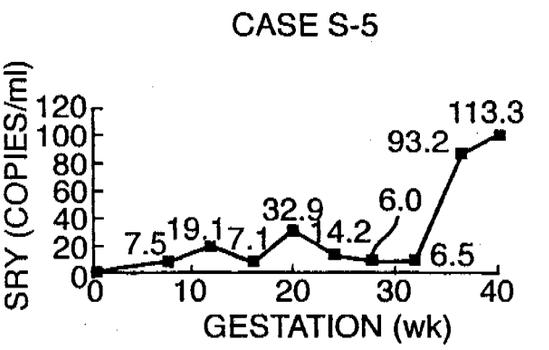


Fig. 4d

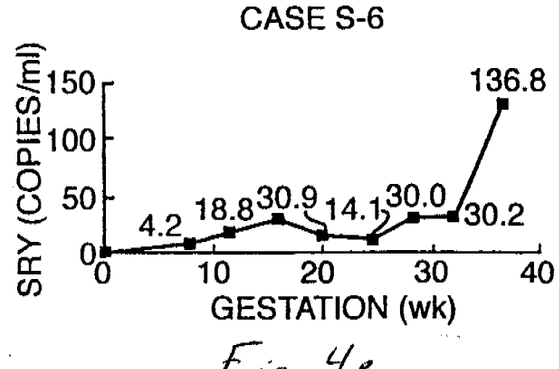


Fig. 4e

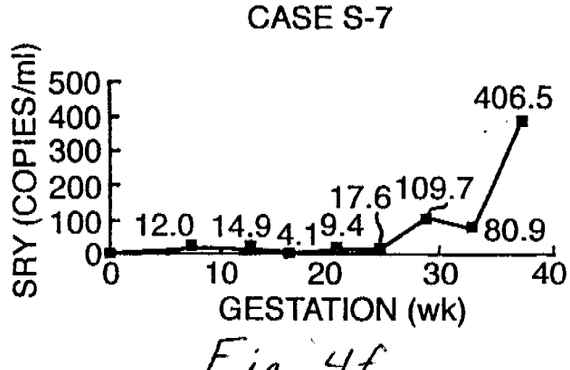


Fig. 4f

Fig.4(Cont.)

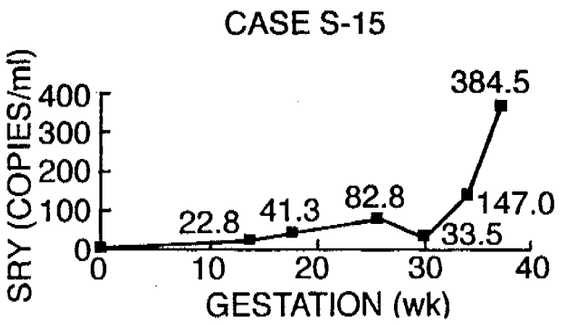


Fig. 4g

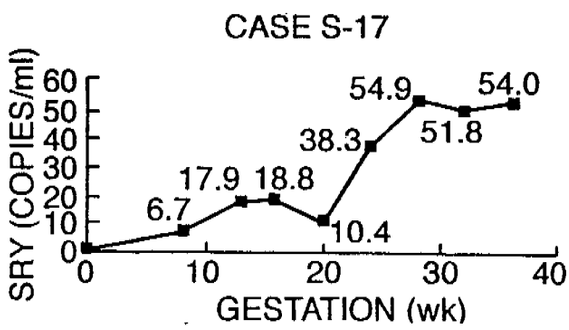


Fig. 4h

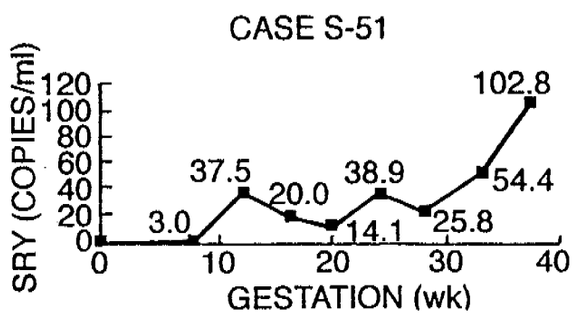


Fig. 4i

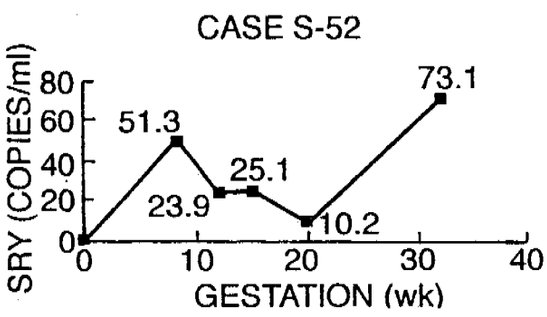


Fig. 4j

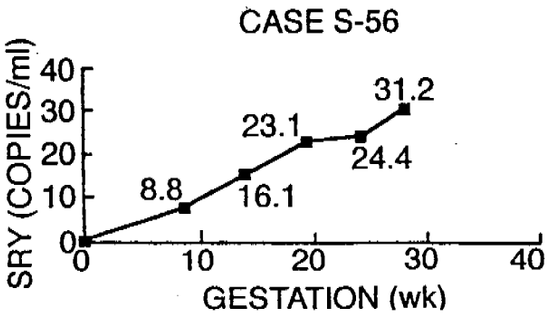


Fig. 4k

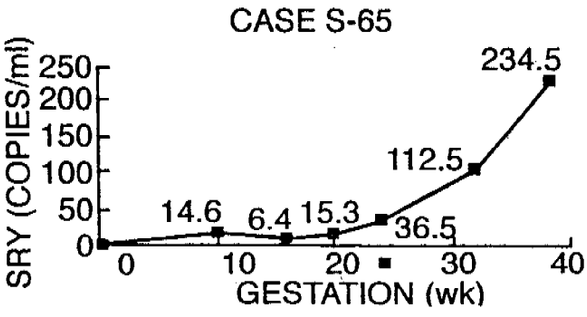


Fig. 4l

Volpe and Koenig, P.C. Revision of PTO/SB/17 (12/99)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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# FEE TRANSMITTAL for FY 2000

*Patent fees are subject to annual revision.*
*Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12. See 37 C.F.R. §§ 1.27 and 1.28.*

**TOTAL AMOUNT OF PAYMENT** ($) $208.00

| *Complete if Known* | |
|---|---|
| Application Number | 09/380,696 |
| Filing Date | November 29, 1999 |
| First Named Inventor | Lo et al. |
| Examiner Name | Enewold, J. |
| Group / Art Unit | 1655 |
| Attorney Docket No. | SHP-PT048 |

## METHOD OF PAYMENT (check one)

1. ☐ The Commissioner is hereby authorized to charge the fees indicated hereon:

Deposit Account Number: 22-0493

Deposit Account Name: Volpe and Koenig, P.C.

☒ Charge Any Deficiency or Credit Any Overpayment in the Total Fees Associated with this Communication — Our Order No. 1822

2. ☒ **Payment Enclosed:** ☒ Check ☐ Money Order ☐ Other

## FEE CALCULATION

### 1. BASIC FILING FEE

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 101 | 690 | 201 | 345 | Utility filing fee | |
| 106 | 310 | 206 | 155 | Design filing fee | |
| 107 | 480 | 207 | 240 | Plant filing fee | |
| 108 | 690 | 208 | 345 | Reissue filing fee | |
| 114 | 150 | 214 | 75 | Provisional filing fee | |

SUBTOTAL (1) ($)

### 2. EXTRA CLAIM FEES

| | | Extra Claims | | Fee from below | Fee Paid |
|---|---|---|---|---|---|
| Total Claims | 28 | - 20** = | 2 | X $9.00 | = $18.00 |
| Independent Claims | 3 | - 3 ** = | 0 | X $39.00 | = 0 |
| Multiple Dependent | | | | | = |

**or number previously paid, if greater; For Reissues, see below

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description |
|---|---|---|---|---|
| 103 | 18 | 203 | 9 | Claims in excess of 20 |
| 102 | 78 | 202 | 39 | Independent claims in excess of 3 |
| 104 | 260 | 204 | 130 | Multiple dependent claim, if not paid |
| 109 | 78 | 209 | 39 | ** Reissue independent claims over original patent |
| 110 | 18 | 210 | 9 | ** Reissue claims in excess of 20 and over original patent |

SUBTOTAL (2) ($) 18.00

## FEE CALCULATION (continued)

### 3. ADDITIONAL FEES

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 105 | 130 | 205 | 65 | Surcharge - late filing fee or oath | |
| 127 | 50 | 227 | 25 | Surcharge - late provisional filing fee or cover sheet. | |
| 139 | 130 | 139 | 130 | Non-English specification | |
| 147 | 2,520 | 147 | 2,520 | For filing a request for reexamination | |
| 112 | 920* | 112 | 920* | Requesting publication of SIR prior to Examiner action | |
| 113 | 1,840* | 113 | 1,840* | Requesting publication of SIR after Examiner action | |
| 115 | 110 | 215 | 55 | Extension for reply within first month | |
| 116 | 380 | 216 | 190 | Extension for reply within second month | $190 |
| 117 | 870 | 217 | 435 | Extension for reply within third month | |
| 118 | 1,360 | 218 | 680 | Extension for reply within fourth month | |
| 128 | 1,850 | 228 | 925 | Extension for reply within fifth month | |
| 119 | 300 | 219 | 150 | Notice of Appeal | |
| 120 | 300 | 220 | 150 | Filing a brief in support of an appeal | |
| 121 | 260 | 221 | 130 | Request for oral hearing | |
| 138 | 1,510 | 138 | 1,510 | Petition to institute a public use proceeding | |
| 140 | 110 | 240 | 55 | Petition to revive - unavoidable | |
| 141 | 1,210 | 241 | 605 | Petition to revive - unintentional | |
| 142 | 1,210 | 242 | 605 | Utility issue fee (or reissue) | |
| 143 | 430 | 243 | 215 | Design issue fee | |
| 144 | 580 | 244 | 290 | Plant issue fee | |
| 122 | 130 | 122 | 130 | Petitions to the Commissioner | |
| 123 | 50 | 123 | 50 | Petitions related to provisional applications | |
| 126 | 240 | 126 | 240 | Submission of Information Disclosure Stmt | |
| 581 | 40 | 581 | 40 | Recording each patent assignment per property (times number of properties) | |
| 146 | 690 | 246 | 345 | Filing a submission after final rejection (37 CFR § 1.129(a)) | |
| 149 | 690 | 249 | 345 | For each additional invention to be examined (37 CFR § 1.129(b)) | |

Other fee (specify) _____

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid — SUBTOTAL (3) ($) 190

| SUBMITTED BY | | | | Complete (if applicable) | |
|---|---|---|---|---|---|
| Name (Print/Type) | C. Frederick Koenig III, Esquire | Registration No. (Attorney/Agent) | 29,662 | Telephone | 215-568-6400 |
| Signature | | | | Date | 9/15/00 |

**WARNING:**

**Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

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# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| **Application Number** | 09/380,696 |
| **Filing Date** | November 29, 1999 |
| **First Named Inventor** | Lo et al. |
| Group Art Unit | 1655 |
| Examiner Name | Enewold, J. |
| Total Number of Pages in This Submission: 20 | Attorney Docket Number: SHP-PT048 |

**ENCLOSURES** *(check all that apply)*

- [x] Fee Transmittal Form
- [x] Fee Attached
- [x] Amendment / Response
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Additional Enclosure(s) *(please identify below)*:

Attachments (6 Articles); Marked Up Drawing sheets (2 pgs.); Abstract (1 pg.)

Remarks

**SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT**

| | |
|---|---|
| Firm or Individual name | C. Frederick Koenig III, Esquire Reg. No. 29,662<br>VOLPE and KOENIG, P.C. |
| Signature | |
| Date | 9/15/00 |

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date: Sept. 15, 2000

| | | | |
|---|---|---|---|
| Typed or printed name | C. Frederick Koenig III, Esquire | | |
| Signature | | Date | 9/15/00 |

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